Remarks/Arguments:

As an initial matter, it is noted that the Supplemental Amendment filed March 6, 2003, submitted claims 26-41 in place of claims 11-25. While the Office Action does not reflect entry of claims 26-41 on the record, the numbering of claims in accordance with the instant amendment takes into account the claims submitted in the Supplemental Amendment. Therefore, the new claims submitted in accordance with the instant Amendment begin with the next highest number, i.e., claim 42.

Claims 42-57, submitted hereby, are pending.

Claims 11-41 are cancelled, hereby, without prejudice or disclaimer.

Present claims 42-44 and 47-57 contain the subject matter of claims 11-13 and 15-25, respectively, revised in order to more clearly define the instant invention, as discussed below. address the issues raised by the present Office Action, as explained below. Likewise, the subject matter of claim 14 is divided into present claims 45 and 46.

Claims 11-25 were rejected under 35 U.S.C. 112, second paragraph, as allegedly being indefinite. Reconsideration is requested in view of the changes to the claims effective, hereby.

Applicants submit that the changes in the claims reflected in the instant amendment resolve the issues raised in the §112, ¶2, rejection. Accordingly, the rejection is in order for withdrawal.

Claims 11-22 and 25 were rejected under 35 U.S.C. 103(a) as being allegedly unpatentable based on the teachings of Guo in view of Ishii and, further, in view of Sobol. Reconsideration is requested. Claims 23 and 24 were rejected under 35 U.S.C. 103 as being allegedly unpatentable

based on Guo in view of Schena. Reconsideration of the aforesaid rejections under §103(a) is requested.

To establish *prima facie* obviousness of a claimed invention, all the claim limitations must be taught or suggested by the prior art. *In re Royka*, 490 F.2d 981, 180 USPQ 580 (CCPA 1974). "All words in a claim must be considered in judging the patentability of that claim against the prior art." *In re Wilson*, 424 F.2d 1382, 1385, 165 USPQ 494, 496 (CCPA 1970). A "ground of rejection is simply inadequate on its face . . . [when] the cited references do not support each limitation of [the] claim." *In re Thrift*, 63 USPQ2d 2002, 2008 (Fed. Cir. 2002). When conducting an obviousness analysis, "all limitations of a claim must be considered in determining the claimed subject matter as is referred to in 35 U.S.C. 103 and it is error to ignore specific limitations distinguishing over the [prior art] reference." *Ex parte Murphy*, 217 USPQ 479, 481 (PO Bd. App. 1982).

The references cited against the rejected claims all relate to the analysis of polynucleotides using oligonucletides. The present claims, on the other hand, are directed to the analysis of polynucleotides using polynucleotides.

Guo describes a similar linker except that it has an oligo(dT) spacer, and the reference teaches attaching short oligonucleotides. The presently claimed invention attaches long polynucleotides and therefore cannot use the oligo(dT) spacer, because this would hybridize with the DNA and, so, would not work. Therefore, one of ordinary skill in the art would not have been motivated to use the linkers of Guo to analyze polynucleotides.

With regard to Sobol, Sobol binds the polynucleotides to a surface. Sobol then tests the polynucleotides with an oligonucleotide. Sobol does not teach or suggest how to test a polynucleotide with a polynucleotide.

Finally, Ishii describes detection of polynucleotides using oligonucleotides. Again there is no teaching or suggestion to detect polynucleotides with polynucleotides.

An advantage of the presently claimed invention is that there is higher sensitivity and higher selectivity of the detection assay.

For a better understanding, Applicants consider it useful to clarify the differences between a probe and a target. In the presently claimed, and every other, microarray system, the probe is defined as a nucleic acid, the identity or quantity of which has to be determined in the microarray experiment. The probe is generated from a sample to be analyzed, the probe is normally transcribed from RNA to cDNA, and the probe is normally labeled. The target (in microarrays) is a nucleic acid that is bound (covalently or no-covalently) to a support. The target, on the other hand, is normally not labeled, the sequence (i.e., identity) of the target is normally known, and (therefore) the target is used to determine the identity or quantity of the probe.

In Guo et al. and many other microarray descriptions, the (known) target is an oligonucleotide having a length between 10 and 70 nt.

Sobol et al. is similar to Guo et al. in that both determe the identity or presence of a nucleic acid of interest. According to Sobol a known target is amplified from a sample. The reference teaches use of an oligonucleotides to determine whether an amplification has occurred or not (Sobol

column 13, line 39 and following). A difference with Guo is that Sobol call the oligonucleotide a "probe," not a target. Sobol (column 13, line 55) describes also a so-called "reverse" dot blot method, where the probe is fixed to a solid support, which essentially is what is done in microarrays.

As such, Sobol et al. and Guo et al. both teach assays involving fixing oligonucleotides to a support surface.

Then, Sobol et al. teaches fixing the amplified DNA to a substrate (Sobol column 14, lines 39-50) and testing the fixed, amplified DNA using a labeled probe (in this case, again, an oligonucleotide, which in microarray literature would be called a target). This is where the difference occurs: Sobol teaches fixing, to a suppot, the long DNA to be tested; whereas, the present claims fix, to a support, long DNA used to test other long DNA.

There is also a difference in that the present claims perform a hybridization between a fixed DNA of > 200 nt with a DNA generated by reverse transcription that is, also, > 200 nt. Sobol and Guo describe the hybridization between a long DNA and a short oligonucleotide. Therefore, in light of Sobol et al. it would have been obvious to attach PCR amplified DNA to a substrate, but it would not have been obvious to link this DNA to a substrate using the linker and spacer used by Guo et al. Following Guo et al. and Sobol et al. it would have been obvious to attach an oligo-nucleotide to test a long DNA, but not to fix a long DNA with the chemistry supposed by Guo et al.

Also, Ishii et al. do not teach or suggest the attachment of longer DNAs but, rather, oligonucleotides.

This point is important, as it is a great difference whether one tries to hybridize selected short oligo-nucleotides with (selected) amplified DNA (no matter which is immobilized) or one tries to hybridize complex DNA mixtures, which can be pre-selected in their sequence due to a reverse transcription to a pre-selected long DNA. The difference is that the reverse transcribed DNA carries all possible nucleotide sequence combinations especially when making a reverse transcription of a RNA mix. That is why one cannot use the chemistry of Guo et al. as the reference uses an oligo(dT) stretch in the linker, which would crosshybridize with complex cDNA mixtures. As Sobol et al. is not suggesting use of long DNA to test their amplified DNA, it is even far less obvious to substitute the Guo chemistry with the chemistry of Ishii (alky-amines) for the attachment of long cDNAs.

The skilled person interested in performing a hybridization assay for complex cDNAs would not have been motivated by Sobol et al. to substitute the oligonucleotides described by Guo et al. with long pre-selected cDNAs, because Sobol et al. describes the fixing of amplified DNA in a completely different application. Sobol et al. even state that it would make sense to fix the oligonucleotides ("reverse" dot blot), but they do not mention at all that it would make sense to attach long cDNAs to test their amplified DNA (still, then, it would not be the same assay as presently claimed). In addition, as Sobol et al. is attaching targets, rather than probes, these targets are not optimized for hybridization detection of long cDNAs, as is the purpose of arrays in the present claims. The amplified DNAs of Sobol et al. have a strongly variable length, which is mostly <200 nt, and only in some cases >200 nt. That is because they have optimized the DNA length in view of optimal PCR-amplification and not in view of a sensitive hybridization assay of complex

cDNAs, again, which highlights the differences in the approach according to the present claims and the approach according to the cited prior art.

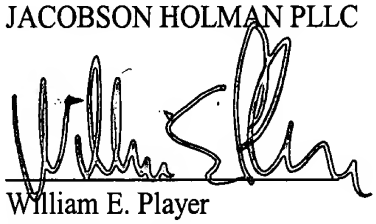
Schena adds nothing to cure the fatal deficiencies in Guo, as set forth above.

In accordance with the foregoing explanation, none of the cited references, taken alone or in combination, teaches or suggests a salient feature (limitation) of the present claims, i.e., in essence, the use of *polynucleotides* to test *polynucleotides*. As such, since the cited references "do not support each limitation" of the present claims, each of the rejections under §103(a) is "inadequate on its face." *Thrift*, 63 USPQ2d at 2008.

Favorable action is requested.

Respectfully submitted,

JACOBSON HOLMAN PLLC

By 

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